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Conference Proceedings

Eighth International Chorea–Acanthocytosis Symposium: Summary of Workshop Discussion and Action Points

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Abstract

Chorea-Acanthocytosis (ChAc) is a rare hereditary neurological disorder characterized by abnormal movements, red blood cell pathology, and progressive neurodegeneration. Little is understood of the pathogenesis of ChAc and related disorders (collectively Neuroacanthocytosis). The Eighth International Chorea-Acanthocytosis Symposium was held in May 2016 in Ann Arbor, MI, USA, and focused on molecular mechanisms driving ChAc pathophysiology. Accompanying the meeting, members of the neuroacanthocytosis research community and other invited scientists met in a workshop to discuss the current understanding and next steps needed to better understand ChAc pathogenesis. These discussions identified several broad and critical needs for advancing ChAc research and patient care, and led to the definition of 18 specific action points related to functional and molecular studies, animal models, and clinical research. These action points, described below, represent tractable research goals to pursue for the next several years.

Keywords: Chorea Acanthocytosis, Neuroacanthocytosis, VPS13, VPS13A, Chorein

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Introduction

The Eighth International Chorea–Acanthocytosis Symposium was held on May 14 and 15, 2016, in Ann Arbor, MI, USA. Previous

conferences were held in Seon, Germany; Montreal, Québec, Canada; London and Oxford, UK; Kyoto, Japan; Bethesda, MD, USA; Ede, The Netherlands; and Stresa, Italy. Two comprehensive summary volumes were among the outcomes of these meetings.^{1,2} The most

Table 1. **VPS13 Nomenclature**

| Gene | Protein |
|------------------------|---|
| <i>S. cerevisiae</i> | |
| <i>VPS13</i> | Vacuolar Protein Sorting-associated protein 13 (Vps13p) |
| <i>D. melanogaster</i> | |
| <i>Vps13</i> | Vacuolar Protein Sorting-associated protein 13 (VPS13) |
| <i>H. sapiens</i> | |
| <i>VPS13A</i> | Chorein Vacuolar Protein Sorting-associated protein 13A (VPS13A) |
| <i>VPS13B</i> | Vacuolar Protein Sorting-associated protein 13B (VPS13B) |
| <i>VPS13C</i> | Vacuolar Protein Sorting-associated protein 13C (VPS13C) |
| <i>VPS13D</i> | Vacuolar Protein Sorting-associated protein 13D (VPS13D) |

Table 2. **Known Vps13p (yeast) Localizations, Functions, and Interactions**

| Localizations | Functions | Interactions |
|--|---|----------------------|
| Late endosome/PVC | TGN to PVC transport | Cdc31p–yeast centrin |
| TGN | TGN homotypic fusion | |
| Nuclear–vacuolar junction | Unknown | |
| Prospore membrane | Prospore membrane maturation and fusion | Spo71p |
| Vacuolar–mitochondrial junction | Mitochondrial integrity | Mcp1p |
| Lipid droplet aggregates | Unknown | |

Abbreviations: PVC, Prevacuolar Compartment; TGN, Trans-Golgi network.

recent neuroacanthocytosis symposium in Ann Arbor was accompanied by an organized parallel patient meeting. It was attended by 16 families with patients affected by chorea–acanthocytosis (ChAc) or McLeod syndrome, and was organized by the Advocacy for Neuroacanthocytosis Patients (www.naadvocacy.org).

The focus of the current scientific symposium was ChAc, functions of the causative protein chorein (encoded by *VPS13A*; Table 1), and related intracellular transport mechanisms (a full list of speakers and topics is available at <https://sites.google.com/a/umich.edu/chac/symposium/home>).

Accompanying the meeting, members of the neuroacanthocytosis research community and other invited scientists met in a workshop format to discuss current progress and critical next steps and experiments needed to better understand ChAc pathogenesis. Topics related to three broad themes were discussed: 1) the burgeoning knowledge of yeast Vps13p function as a foundation for

understanding *VPS13A* biology and ChAc pathogenesis; 2) the status of animal models of ChAc; 3) critical needs in ChAc clinical research and patient care.

This document summarizes the workshop discussion and sets forth a list of tractable action points for the ChAc research community. Readers are directed to previous review articles and volumes for comprehensive overviews of the field.^{1–3}

Current understanding of VPS13 function: insights from yeast models

Dr. Robert Fuller (University of Michigan) led a discussion outlining current knowledge regarding the known functions of the Vps13 protein (Vps13p) in yeast. Extensive work in yeast has provided a large number of identifiable Vps13p cellular localizations, functions, and interactions (Table 2, Figure 1). The yeast work is a rich source of hypotheses about the functions of mammalian VPS13 homologues.⁴ Although there is

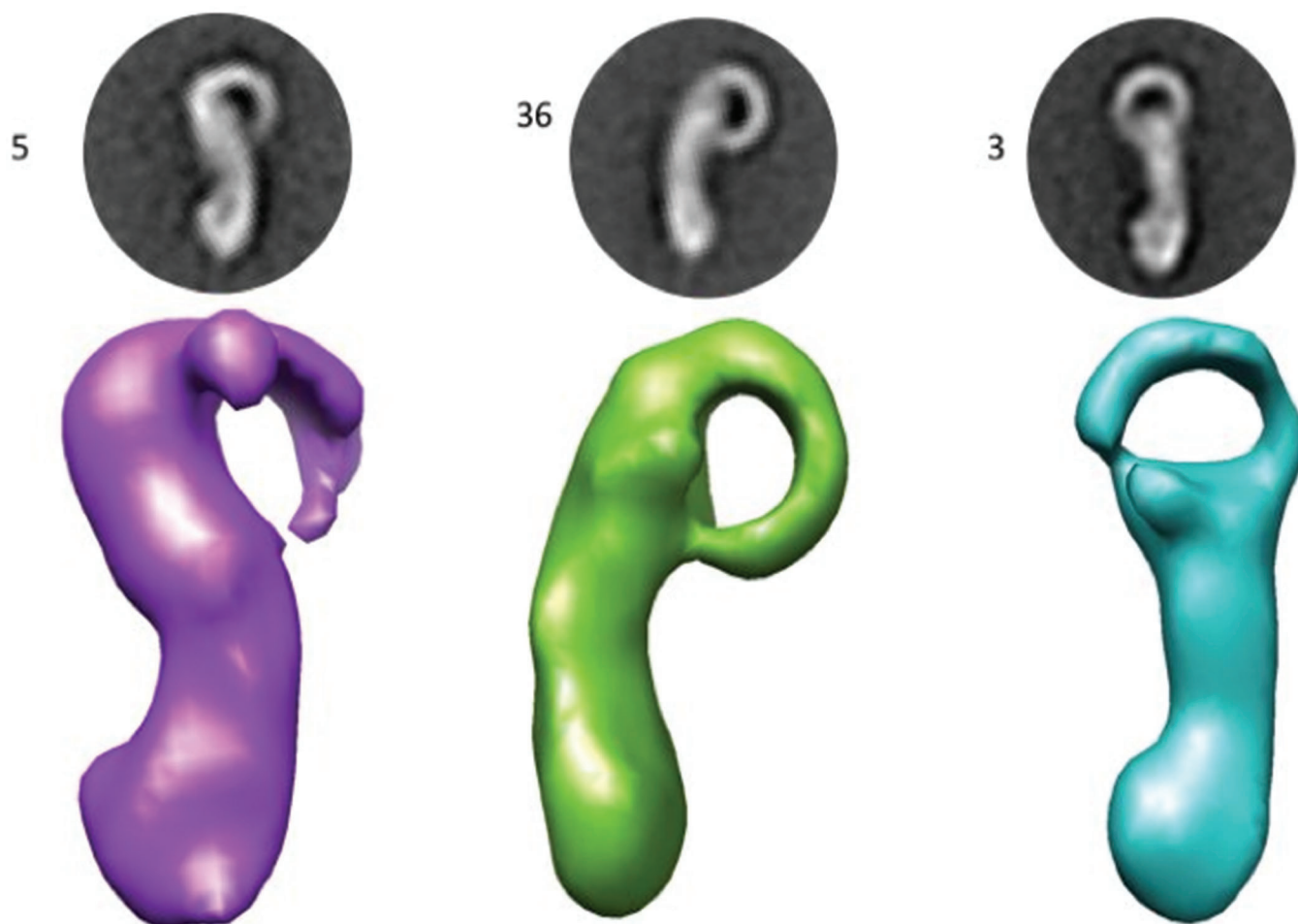


Figure 1. Three-dimensional Architecture of Purified Yeast Vps13 Protein. The Vps13 structure was determined using negative-stain electron micrograph image analysis. Further biochemical and structural analyses of yeast Vps13p are described in reference 19.

Box 1. Example of a critical experiment (Action point 1): characterize the rare human missense mutations that result in disease, but do not cause loss of protein product

Discussions of yeast Vps13p studies led to the definition of multiple proposed experimental questions aimed at understanding the *localizations*, *functions*, *interactions*, and *cellular roles* of VPS13A in human and other mammalian cells. The experimental goals relating to these characteristics are outlined as Action points 1–10 above.

A recent estimate, based on more than 100 cases of already published and unpublished data, is that at least 95% of human VPS13A mutations lead to loss of the protein product chorein when patient cell lysates are analyzed by Western blot.^{6–10} This demonstrates that VPS13A loss of function is a primary pathogenic mechanism causing ChAc. The small number of patients with point mutations, but whose samples contain measureable chorein levels, present with typical clinical symptoms and disease progression, suggesting that their mutations render chorein non-functional. Defining the effects of these missense mutations will be a critical step toward understanding chorein structure–function relationships.

To achieve these goals, the fundamental effects of each known mutation must be established, including determining the level of RNA expression, protein quantity, and whether alternative proteins are produced. The antibodies previously used recognize the N-terminal portion of the protein (approximately the first 300 amino acids of the 3,174 amino acid chorein protein), but other available antibodies recognizing the C-terminal and internal sites are also available. Antibodies to the C-terminal portion of chorein are likely the best option for diagnostic purposes.

Fundamental cell biological questions may be answered by introducing these point mutations into yeast (if the residue is conserved), *Drosophila*, or induced pluripotent stem cells. These studies could be performed in parallel with lipidomic studies of VPS13A knockout cells and proteomics of wild-type cells. In this manner, the point mutants could be used to understand fundamental biology and could provide a more comprehensive understanding of this complex protein.

significant understanding of Vps13p in yeast, the extent to which these reflect the biological consequences of chorein function (and loss of function)

in mammalian cells and human tissue is unknown, and represents a major gap in the field (Box 1).

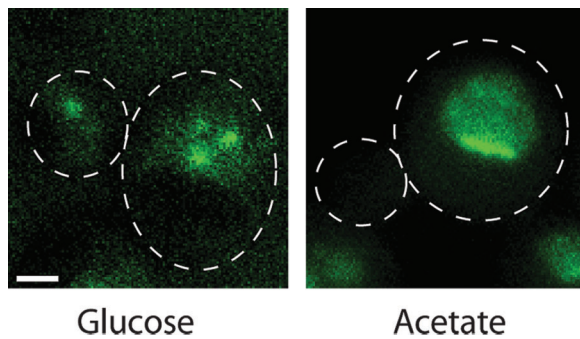


Figure 2. Yeast Vps13p Localization. Yeast Vps13 localization is dependent on the carbon source. In cells grown in glucose (left), Vps13–GFP is present in cytoplasmic punctae that predominantly co-localize with endosomal markers. When cells are grown in the non-fermentable carbon source acetate (right), Vps13–GFP concentrates at the membrane contact site between the nuclear and vacuolar membranes. Dashed lines indicate the outlines of the budding cells. Scale bar = 5 μ m. Further details regarding Vps13 localizations have been previously published.^{5,18}

Yeast Vps13p is prominently localized to the late endosome/prevacuolar compartment (LE/PVC), trans-Golgi network (TGN), peroxisome, autophagosomes, and at membrane contact sites (Figure 2), including mitochondrial–endosomal junctions, nuclear–vacuolar junctions, and vacuole–mitochondrial junctions (vCLAMP, vacuole and mitochondria patch).⁵ These widespread localizations position Vps13 to serve potentially diverse cellular roles, including vesicular transport, TGN–LE transport, TGN homotypic fusion, prospore membrane maturation, and maintenance of mitochondrial integrity in pathways related to the endoplasmic reticulum–mitochondria encounter structure (ERMES) complex.

Although these roles are important, there are a number of additional interactions to consider. For example, recent data suggest that Vps13p may stimulate the synthesis of several lipids, including PI(4)P and PI(4,5)P₂, and phosphatidic acid, which are rich in the prospore membrane, and which also bind Vps13p. This suggests a possible positive feedback loop in which Vps13p stimulates synthesis of lipids, to which it also binds, leading to the promotion or organization of structures. It is not fully understood how the protein stimulates this lipid synthesis, but studies suggest potential recruitment of phospholipase D (Spo14p) to the prospore membrane. As such, Vps13p may not solely create junctions or catalyze lipid transfers, but could also initiate or potentiate lipid synthesis. Investigating these functions may uncover potential enzymatic targets amenable to drug therapy.

In the context of disease, a fundamental question is which Vps13p functions are homologous in mammalian cells, particularly neurons, and which functions are required for cell survival. In this context, the yeast work is a solid foundation for hypothesis generation. The association of yeast Vps13p with virtually all cellular organelles is a unique property of the protein in comparison to other secretory pathway (Sec)/vacuolar protein sorting (Vps) proteins. It is unclear whether Vps13p performs the same common fundamental function in each compartment and context, or distinct functions in different subcellular contexts. It is currently unknown whether the mammalian

VPS13 homologues each have individual or multiple roles and localizations in mammalian cells, if there are tissue- or cell type-specific differences in these characteristics, and if specific functions are important for disease phenotypes. Therapeutic approaches targeting specific compartments could be considered once these features are established.

An example of a yeast finding that generates hypotheses about the functions of mammalian homologues, and that could lead to a therapeutic target, is the role of Vps13p in TGN to PVC transport. An *in vitro* system reconstituting TGN to PVC transport has been used to infer VPS13p functions. In cell-free TGN to PVC transport, there is a kinetic lag that implies the formation of an intermediate that functions during a later step. In a typical vesicular transport reaction, such a lag might correspond to transport vesicle formation. Unpublished data presented at the workshop suggest that Vps13p and the phosphatidyl inositol/phosphatidyl choline transport protein, Sec14p, both function during this lag. The role of Sec14p in stimulating synthesis of PI(4)P at the Golgi suggests that the lag may represent the rebuilding of PI(4)P pools on TGN membranes. Because there is evidence that Vps13p stimulates PI(4)P synthesis on prospore membranes, it may similarly stimulate PI(4)P synthesis in the TGN to PVC reaction. A number of possible mechanisms could explain this putative role (e.g., interaction with PIK1 or blockade of phosphatase function), which begins to invoke potentially druggable enzymes. However, the relevance of these pathways to human cells is unknown.

As another example, introduction of three different point mutations found in ChAc patients into the yeast Vps13 results in separation-of-function alleles. These mutations show specific defects in the mitochondrial integrity aspect of Vps13 function. The common loss of this specific activity in multiple alleles raises the possibility that the human disease phenotypes are related to mitochondrial dysfunction.⁵

Further studies using this type of pathway-oriented approach in yeast, red blood cells (RBCs), and other model systems (as described below) may implicate additional potentially druggable targets. Beyond *in vitro* studies, these putative pathways could be manipulated in cell and animal models as a next step toward viable therapies.

Action points: VPS13 functional studies

1. Characterize the rare human missense mutations that result in disease, but do not cause loss of protein product.
2. Characterize chorein localization in mammalian/human cells.
3. Define associated proteins/complexes.
4. Establish functional readouts/assays for mammalian cells.
5. Define the structure of human chorein isoforms.
6. Perform unbiased lipid profiling studies in mutant and control cells.
7. Perform yeast synthetic tether experiments to model roles at junctions.
8. Assess mitochondrial (and other organelle) function/dysfunction in human cells.
9. Characterize autophagosome–lysosome fusion
10. Consider antisense transcript in knockout models

Box 2. Example of critical experiment (Action point 12): genetic and drug screening studies in *Drosophila* model

The *Drosophila VPS13* knockout model exhibits several unique features that position it as a powerful screening tool to examine genetic interactors, molecular pathways, and novel drug targets. The sudden death phenotype is a distinct and easily quantifiable end point that provides a powerful advantage over other model systems. One approach is to use ethyl methanesulfonate mutagenesis or interference RNA to screen for extragenic enhancers and suppressors. If fundamental pathways are uncovered that protect from or accelerate premature death, further histopathological studies could be performed to determine if manipulation of key pathway components prevents the formation of neuronal vacuoles. In conjunction with findings from yeast work, this may facilitate identification of key pathways and therapeutic targets. This would lead to further studies in mammalian cells, mouse models, and human samples, and may attract more researchers to the field.

Box 3. Defining the natural history and progression of ChAc

The first clear clinical goal is to systematically define the natural history of ChAc. Common standards and rating scales need to be created and a significant number of patients should be evaluated yearly. A wide range of clinical and imaging data should be collected. Additional presymptomatic identification and phenotypic characterization of mutation carriers would assist in understanding the emergence and progression of ChAc features. As a model, Dr. Landwehrmeyer discussed the ENROLL-HD study, a large observational natural history study for Huntington's disease. There is already an effort to collect phenotypic data in ChAc patients, which is structured as a submodule of the natural history registry in the European HD network (www.euro-hd.net/html/na/submodule). While some data have been collected, several obstacles (notably its voluntary character and the rarity of ChAc) inhibit this effort. International accumulation of data is required because of the rarity of ChAc, and is slowed by the need for multiple ethics boards approvals, preventing individual clinicians and researchers from contributing data. An important goal would be to build on this network. Several logistical issues would need to be considered, including how to make data widely available, how to use the network as a recruitment tool for future studies, and creating interfaces that will be accessible to both participants and researchers in multiple languages.

Animal models

Given the rarity of ChAc and related disorders and the relative difficulty of clinical research, valid animal models are a high priority for the field. Prior work has included mouse, tetrahymena,¹¹ and dictyostelium¹² models. Drs. Ody Sibon (Groningen) and Andreas Hermann (Dresden) led a discussion of the initial findings from newly developed *drosophila* and mouse knockout models.

Dr. Sibon described a new *Drosophila VPS13* knockout model that is characterized by age-associated neurodegeneration, reduced locomotor function in climbing assays, and premature death, which are partially rescued with human VPS13A overexpression. This represents the first ChAc model to exhibit overt neurodegeneration associated with motor behavioral abnormalities.²⁰ One notable feature of the *drosophila* model is abrupt early mortality, which should be considered further as a way to examine underlying pathophysiological mechanisms and as a screening tool (Box 2). Further studies aiming to identify rescue interventions of the fly model could provide a link toward human therapies.

Dr. Hermann (Dresden) and Dr. Lucia De Franceschi (Verona) discussed early work from *VPS13A* knockout mouse models (in addition to a published, but not generally available prior mouse model),^{13,14} including conditional knockout lines. Some similarities emerge through this work, including infertility (particularly in male mice) and impaired autophagy. To date, no overt neurological phenotypes have been observed in these mouse lines, and neuropathological examinations have not been completed systematically.

Pathway-based approaches have been useful to generate hypotheses in animal modeling research. For example, studies of RBCs from ChAc patients provided first insights into possible functions of human chorein. While RBC membrane lipid composition appears essentially normal, patient erythrocytes demonstrate increased Lyn kinase activity.¹⁵ Unpublished data presented at the workshop demonstrated phenotypic

rescue in RBC and patient-derived neuronal cells with Lyn kinase inhibition, suggesting Lyn kinase inhibition as a potential druggable target.¹⁶ It is important to confirm if these abnormalities are present in neurons and if they warrant future rescue studies with Lyn kinase inhibitors. Compensation by other VPS family members, genetic background effects, and age should be considered in the evaluation of mouse models.

Action points: ChAc animal model studies

11. Definitively characterize behavioral and neuropathological phenotypes in new animal models.
12. Perform genetic and drug screening studies in *Drosophila* model.
13. Complete neuropathology and lipid profiling studies in *VPS13* knockout mice.

Clinical research and patient care

The final discussion was led by Drs. Bernhard Landwehrmeyer (Ulm) and Adrian Danek (Munich) and addressed our understanding of the clinical features of ChAc.³ The ultimate goal of clinical research in ChAc is to produce useful interventions and disease-modifying therapies. A detailed understanding of phenotypic variation and natural history is needed for planning good intervention studies (Box 3). Because ChAc is a very rare disease, intervention studies will be handicapped by very small numbers of participants. Studies using clinical endpoints must be based on well-characterized clinical instruments and will probably require very large predicted intervention effect sizes. Development of efficient biomarkers reflecting disease activity will be crucial to circumvent these problems.

Another key objective of a clinical research network is the further collection of patient and control biosamples for biomarker research. Ideally, this would include a wide range of fluids (blood, serum, cerebrospinal fluid), tissues, and post-mortem specimens. Facilitation

of biomarker studies should be a high priority. An accessible repository, building upon a collection based at the neuropathology institute of the University of Munich (blood and DNA samples, ChAc muscle biopsies and brain tissue) will facilitate hypothesis-based, goal-directed studies with appropriate materials. These materials are crucial for validation of pathogenesis and biomarker studies from animal models. Other related disorders, including McLeod syndrome, diseases based on mutations of *VPS13C*¹⁷ and *VPS13D* (poster at this symposium), and other HD-like phenotypes could be included, particularly because these patients are being cared for by many of the same physicians as ChAc patients.

It is possible that some of these activities could be done in parallel with efforts in HD research, given the similar clinical context. Working within the structures already in place for the study of HD will increase geographical coverage, providing medical professionals who can assist and perform quality monitoring, thereby creating more and higher quality data for collaborative studies. Importantly, this along with the longstanding support and extensive network activity by the Advocacy for Neuroacanthocytosis Patients would also facilitate recruitment of patients for imaging studies and for donation of biomaterials.

Bench researchers working on *VPS13A* biology or with animal models should think actively about biological features in their studies that could translate to markers of underlying pathologies and potential biomarkers in patients. Plausible, well-defined functional readouts are needed. Therapeutics should be based on the observed pathogenesis and follow the identification of targets, rather than focusing on untargeted broad high throughput approaches. Development of good biomarkers is challenging and this will require many levels of collaboration between caregivers, clinical research, basic research, and translational studies.

In parallel with this research network, another important project would be to develop an internet platform for clinicians to easily discuss experiences with management of ChAc patients. Because performing multiple clinical trials is not feasible, sharing of clinical experience and discussions among clinicians, patients, and caregivers offers the most plausible route for near term improvement of the care of ChAc patients.

Action points: clinical care and research

14. Define natural history and progression of ChAc.
15. Develop standard rating instrument(s).
16. Develop a well-curated biorepository.
17. Conduct prospective, focused biomarker studies.
18. Further develop an internet-based resource and exchange for physicians and medical professionals who assist patients.

Summary

The workshop discussions identified three broad critical needs for advancing ChAc research:

- i. Defining *VPS13A* functions that are critical to neuronal function and survival.
- ii. Definitive evaluation and exploitation of emerging animal and cell models, including human cell models.

- iii. Development of a comprehensive clinical research database, including a well curated biorepository, particularly with a view to defining suitable biomarkers.

ChAc research in the next several years should focus on these needs and attempt to address the action points described above.

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